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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/072,036	02/05/2002	Ole Thastrup	16778.5a.1.1	3012

22913 7590 02/19/2009

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
02/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/072,036	THASTRUP ET AL.	
	Examiner	Art Unit	
	MICHAEL BURKHART	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-54 and 73-82* is/are pending in the application.

4a) Of the above claim(s) *81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-54, 73-80 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 3/27/2008 is acknowledged. After entry of the amendment, claims 44-54 and 73-82 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

Applicant's election without traverse of the species of "object classification" in the reply filed on 11/26/2008 is acknowledged.

Claim 81 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/26/2008.

Claim Objections

Claim 75 is objected to because of the following informalities: "incubating" in line 2 should be "incubated." Appropriate correction is required.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the terms "automated image acquisition", "well plate" and "substantially the entire protein", recited in claims 73, 75 and 79 respectively, are not found in the specification.

Claim Rejections - 35 USC § 112

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons made of record in the Office Action dated 5/30/2007, 12/31/2007, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 3/27/2008 have been fully considered but they are not persuasive. Applicants essentially assert that support for this limitation is found in ¶ [0118] of the published application, which discloses the use of compounds prepared by "organic synthesis." This assertion is not convincing. The term "synthetic compounds" is much broader than "organic compounds." Organic compounds are a broad class of compounds comprising carbon, whereas inorganic compounds are those broadly classified to be of mineral origin. Both organic and inorganic compounds are considered to be included in the genus of "synthetic compounds" : e.g. common salts are synthetic compounds (e.g. Rochelle salt synthesis) but most, if not all, are not organic compounds. Thus, a teaching of synthesizing organic compounds cannot provide support for the broad genus of synthetic compounds.

Claim Rejections - 35 USC § 102

Claims 44-52, 73, 77-80 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Htun et al (PNAS, 1996, cited by applicants, IDS of 2/5/2002) as evidenced by Carey et al (1996, of record) or Agarwal (Pharmacol. Ther., 1996). **This rejection is maintained for reasons made of record in the Office Action dated 12/31/2007, and for reasons set forth below.**

Regarding the amendments to the independent claims 44-46, these appear almost semantic in nature given the previous claim language and the teachings of the prior art. "Screening" a library of compounds necessarily comprises "determining" whether or not a given library member has a function or effect. Otherwise, why else perform the screening if nothing is to be "determined?" For reasons set forth in the previous Office Action, Htun et al clearly "determined" (i.e. "ascertained" according to applicants definition of "determine", page 11 of the response dated 3/27/2008) that GR-GFP was or was not translocated in response to several steroid library members. This is all that is required to meet the claim step (c) in, for instance, claim 44.

Regarding new claim 73 and 80, the term "automated image acquisition" is not defined (or even recited) in the specification. Applicants point to ¶ [0034] for support of "automated image acquisition", however, this ¶ broadly states that the "apparatus system" is automated. Thus, the term "automated image acquisition" is broadly interpreted to include literally any involvement of a computer or electronic system to "automate" image acquisition. See also ¶ [0033] of the published application, in particular the last three lines. In Fig. 5 of Htun et al, it is

taught that digital images are imported and manipulated in a computer, which computer then used ANALYZE software to "acquire" a three dimensional image.

Regarding new claim 77, Htun et al teach the selection of cells expressing GR-GFP by the use of magnetic beads and amounts of luciferase and CAT activity. See page 4846, first column, first full ¶ and the second column, last ¶ to page 4847. Absent a limiting definition of "stable" transformation in the specification, the expression of GR-GFP for the time periods needed for the experiments of Htun et al is considered "stable."

Regarding new claims 78 and 79, it has been explained that GR-GFP fusion protein is a subunit of a protein complex. Furthermore, the specification does not provide a definition of the term "substantially the entire protein", thus the term is given a broad interpretation to include the GR-GFP fusion protein as a subunit of the receptor/steroid component of the signaling pathway. GR inherently binds steroid ligands, such as those used by Htun et al for reasons of record.

Regarding new claim 82, the specification provides no limiting definition of "spatial frequency method", "object finding" or "object classification." A "spatial frequency" analysis of digital images is considered to be the measurement of how often a structure repeats itself per unit of distance (Bar, 2004). Using such information for the GR-GFP fluorescent signals, it is considered Htun et al "found" or "classified" GR-GFP (an "object") in the digital images of, at least, Figs. 4 and 5. Fig. 5 represents multiple images rendered to form three-dimensional models of cell nuclei containing the GR-GFP, with GF-GFP measured across a given distance, i.e. 30 μm.

Response to Arguments

Applicant's arguments filed 3/27/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the compounds screened by Htun et al had a known activity with GR; 2) the cells used by Htun et al were not fixed or evaluated in a micro-well plate; 3) the screening process was done manually; 4) there is no motivation to use Htun et al for screening because the steps of Htun et al are manual as opposed to automated screening; 5) 10% transient transfection is not adequate for screening; 6) Carey and Agarwal et al do not teach screening, only teach manual image acquisition, only teach 30% transfection, and thus do not support the teachings of Htun et al; 7) in view of the Ireland declaration, the teachings of Htun et al should not be considered screening a library; 8) because the compounds used by Htun et al had a known effect on GR, they are not to be considered to anticipate the instant method steps; 9) Htun et al does not teach that translocation of a subunit of a component in response to a compound can be used to determine a biological effect or function on the subunit.

Regarding 1) and 8), that the compounds used by Htun et al had a known effect on GR is stipulated. However, the actual molecule used by Htun et al was GR-GFP, not GR. The effect on GR-GFP of these compounds was unknown. Furthermore, applicants appear to argue this very point by quoting sections of Htun et al (page 9 of the response, quoting page 4849 of Htun et al) where it is taught that the effect of these ligands on GR-GFP was unknown, hence the need to do the screening.

Regarding 1) - 6) and 8), in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., screening compounds with unknown effects, fixed cells, using a multi-well plate, automated screening, stable transfection) are not recited in the rejected claim(s). Although the

claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further regarding 3) and 6), it was explained above why Htun et al is considered to use "automated image acquisition", which is only a limitation in claim 73.

Further regarding 4), motivation is not a concern in anticipation rejections.

Further regarding 5), as explained above, transfected cells were selected from non-transfected cells using magnetic beads and luciferase expression. Based upon the successful results of Htun et al in screening compounds for the ability to induce GR-GFP translocation, this is considered to be adequate for screening. Applicants point to no passages in Htun et al that teach only 10% of the cells expressing GR-GFP were used for the screening assays. In fact, applicants point to no teachings of only 10% of cells being transfected transiently. What is taught, in the ¶ bridging the first and second columns of page 4847 through the second column, is that all of the cells that express GR-GFP were functional in response to dexamethasone. This was more than adequate for Htun et al to determine the effects of the compound library on GR-GFP.

Further regarding 6), Carey and Agarwal et al are not relied upon to teach screening or any other claimed method step. These references are only used to provide inherent teachings of GR being a subunit of an intracellular component. This is not a 35 USC 103 rejection, hence, there is no need to rely upon Carey or Agarwal et al to teach a claim limitation, only to show that the limitations taught by Htun et al have an inherent property. This inherency is not disputed by applicants.

Regarding 7), the compounds of Htun et al meet all the requirements of a compound library as set forth in the Ireland Declaration. See the previous Office Action. Applicants point to nothing in the Ireland Declaration that is not met by the teachings of Htun et al. The actual molecule used by Htun et al was GR-GFP, not GR. The effect on GR-GFP of these compounds was unknown. Each compound was systematically tested for the ability to translocate GR-GFP, i.e. a "particular purpose", as argued by the Ireland Declaration.

Regarding 9), such assertions, unaccompanied by any reasoning or fact, are not convincing in light of the teachings of the prior art set forth above.

Claim Rejections - 35 USC § 103

Claims 44-52, 73-80 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Htun et al (PNAS, 1996, of record) as evidenced by Carey et al (1996, of record) in view of Agarwal (of record, 1996), Sonenberg et al (5,874,231, of record) and Dunlay et al (U.S. 5,989,835, e.f.d. 2/27/1997). **This rejection is maintained for reasons made of record in the Office Action dated 12/31/2007, and for reasons set forth below. New claims and prior art have been added due to amendment of the claims.**

Regarding the amendments to the independent claims 44-46, these appear almost semantic in nature given the previous claim language and the teachings of the prior art. "Screening" a library of compounds necessarily comprises "determining" whether or not a given library member has a function or effect. Otherwise, why else perform the screening if nothing is to be "determined?" For reasons set forth in the previous Office Action, Htun et al clearly "determined" (i.e. "ascertained" according to applicants definition of "determine", page 11 of the

response dated 3/27/2008) that GR-GFP was or was not translocated in response to several steroid library members. This is all that is required to meet the claim step (c) in, for instance, claim 44.

Regarding new claim 73 and 80, the term "automated image acquisition" is not defined (or even recited) in the specification. Applicants point to ¶ [0034] for support of "automated image acquisition", however, this ¶ broadly states that the "apparatus system" is automated. Thus, the term "automated image acquisition" is broadly interpreted to include literally any involvement of a computer or electronic system to "automate" image acquisition. See also ¶ [0033] of the published application, in particular the last three lines. In Fig. 5 of Htun et al, it is taught that digital images are imported and manipulated in a computer, which computer then used ANALYZE software to "acquire" a three dimensional image. Furthermore, Dunlay et al teach the automated acquisition of digital images from large numbers of wells comprising fluorescently labeled reporter molecules. See the abstract, col. 3, line 8 to col. 8 and the correlating figures. One such application is scanning for translocation from the cytoplasm to the nucleus (col. 7, lines 47-63).

Regarding new claims 74 -76, neither Htun, Agarwal nor Sonenberg et al teach fixation of cells, and Carey et al teach fixation for immunostaining. Neither Htun, Agarwal nor Sonenberg et al reasonably teach the use of well plates for the incubation of cells with compounds of the library. Carey et al teaches 2-well slides for this purpose (page 986, second column, third full ¶).

Dunlay et al teach the fixation of cells for their automated methods of screening. See Example 1 and the passages cited above.

Regarding new claim 75, the term "well plate" is not defined in the specification. All that is found in the passage that applicant indicate (¶ [0131]) provides support for this term are the use of 96 well plates. Thus, the term "well plate" is given a broad interpretation to include any tissue culture plate or device that comprises a well. Dunlay et al teach the use of 96 or 384 well plates in, at least, the abstract. Also see Dunlay et al Example 1 wherein incubations with agonists or antagonists are done in the 96 well plates.

Regarding new claim 82, for reasons set forth above, "spatial frequency" is considered to be the measurement of how often a structure repeats itself per unit of distance (Bar, 2004). Dunlay et al teach that their methods may also be used to measure the spatial frequency, or distribution, in fluorescently labeled cells (col. 2, first ¶). Such information is more specifically used in an automated fashion by software to find or classify objects such as nuclei. See col. 5, line 55 to col. 8, in particular col. 7, lines 11-20.

The claimed methods are essentially disclosed by Htun, Agarwal and Sonenberg et al, with the exception of using fixed cells and multi-well plates. The ordinary skilled artisan, seeking methods to study the biology of the GR receptor, or to identify agents with antiglucocorticoid activity, would have been motivated to use the methods taught by Htun, Agarwal and Sonenberg et al with the methods of Dunlay et al because Dunlay et al teaches their method to be useful and efficient in screening large numbers of compounds for an effect upon fluorescently labeled cells (e.g. GFP reporter molecules or fusion proteins, col. 4 lines 23 - 29), which may include translocation to the nucleus. It would have been obvious for the skilled artisan to do this because of the known benefit of maximizing efficiency of experiments when screening large numbers of compounds, as taught by Dunlay et al (e.g. col. 1, lines 9 - 30).

Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicant's arguments filed 3/27/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Agarwal et al does not teach a GR-GFP fusion protein or screening compounds; 2) Sonenberg et al does not teach a GR-GFP fusion protein, translocation, or screening compounds; 3) the combination of Htun, Agarwal and Sonenberg et al is impermissible hindsight, and that there is no valid reason to combine these references; 4) Htun et al do not teach GR antagonists to be involved in translation from mRNA to DNA; 5) the combined references do not teach the amended claim language of claims 44-46.

Regarding 1)- 4) in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further regarding 3), the reasoning to combine the references was clearly stated in the previous Office Action, and did not require any teachings of GR-GFP translocation by Agarwal and Sonenberg et al (it is taught by Htun et al). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be

recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Further regarding 4), this reasoning is unclear. mRNA is not translated to DNA. A central tenet (perhaps a scientific law) in biology is that mRNA is transcribed from DNA. mRNA is then further translated into proteins in the cytoplasm.

Regarding 5), this issue is addressed at the beginning of this rejection and in the 35 USC 102 rejection above.

Claims 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Htun et al, Carey et al, Agarwal, Sonenberg et al and Dunlay et al as applied to claims 44-52, 73-80 and 82 above, and further in view of Cormack et al (Gene, 1996, of record). **This rejection is maintained for reasons made of record in the Office Action dated 12/31/2007, and for reasons set forth below. New prior art have been added to the rejection above due to amendment of the claims.**

Response to Arguments

Applicant's arguments filed 3/27/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Cormack does not cure the deficiencies of Htun, Carey, Sonenberg and Agarwal et al.

Regarding 1), for reason set forth above, the prior art relied upon is not deemed to have any deficiencies.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL BURKHART whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633